

The Conservative Treatment of Myasthenia Gravis

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SUMMARY

Neostigmine is at present the mainstay in treatment of myasthenia gravis. Adjuvant therapy with ephedrine, potassium chloride, or guanidine is recommended. Urecholine,® also used as an adjuvant, is still in the experimental stage and should only be given by one acquainted with its properties and toxic effects. Di-isopropylfluorophosphate and tetraethyl pyrophosphate likewise are still in the experimental stage. Since they are extremely toxic and unstable, general use of them is discouraged until further experimental and therapeutic studies are completed. The results of thymectomy and radiation of the thymus are equivocal and these procedures should be reserved for severe cases which should be selected only after a thorough study.

THE modern treatment of myasthenia gravis is based on knowledge of the synaptic transmission of motor impulses at the myoneural junction by acetylcholine. Since Walker's discovery that physostigmine and neostigmine improved the symptoms of myasthenia, it has been assumed that this disease might be explained in terms of curarizing effect.^{22, 23} Curare and quinine exaggerate the symptoms of myasthenia gravis.^{1, 10} On the other hand, drugs which inhibit the enzyme cholinesterase and which therefore serve to protect acetylcholine are beneficial in myasthenia gravis. These facts have lent credence to the theory of curarizing effect. The precise reason for the failure of synaptic transmission, however, remains obscure.

More recent evidence has suggested that myasthenia is caused by a deficiency of acetylcholine, that is, by "cholinergic insufficiency."^{3, 12} Treatment today is based on the concept that the disease is caused either by curarizing effect or by cholinergic insufficiency, with the additional postulation that one or the other of these theoretical causes might stem from thymic or endocrine disturbances.

The drugs which act as cholinesterase inhibitors (decurarizing effect) are prostigmine bromide, neostigmine (prostigmine methylsulfate), potassium chloride, ephedrine sulfate, and guanidine.^{7, 14, 19, 20}

Neostigmine is the most effective drug in the therapy of myasthenia gravis and, because it is also relatively non-toxic and safe, is the drug of choice. The dosage may vary from 15 to 30 mg. (one or

two tablets) two or three times daily, in mild cases, to as high as 30 mg. six times daily in more severe cases.²¹ If the patient has difficulty starting oral medication in the morning or tends to choke with eating, a combination of oral and parenteral administration may prove of value. In this case, the usual oral dose should be supplemented with 0.5 to 1.0 mg. of neostigmine given intramuscularly in the morning and one hour before meals.²⁰ In severe cases, intramuscular administration may have to be relied upon. The dosage may vary from 0.5 to 2.5 mg. of neostigmine as required. Parenteral doses as high as 1.5 mg. hourly have been reported.²⁰ The emergency treatment of myasthenia in severe exacerbations consists of 1 to 2 mg. neostigmine given intravenously. The intelligent patient, under supervision of a physician, will soon learn to vary the dosage, both oral and parenteral, according to the severity of symptoms. The undesirable gastrointestinal side-effects of neostigmine are adequately controlled by atropine sulfate. In mild cases tincture of belladonna gives good results.⁹ In more severe cases, where parenteral administration of neostigmine is required, atropine sulfate (0.6 mg.) should accompany the neostigmine injection.

As neostigmine is an agent of transient action, adjuvants are required to prolong its effect. Ephedrine, potassium, and guanidine are useful in this connection. Ephedrine sulfate, in doses of from 8.0 to 24.0 mg. two or three times daily, is recommended.⁸ Potassium chloride must be given in doses of from 4 to 6 gm. six times a day.¹⁴ The gastrointestinal and urinary side-effects of potassium therapy may be reduced if it is taken in specially prepared egg-nogs, orange juice, or tomato juice.¹⁹ The results of guanidine therapy have been equivocal. The usual recommended dose is from 10 to 25 mg. per kilogram of body weight, but in severe cases from 20 to 50 mg. per kilogram of body weight daily, administered in three divided doses. may be necessary.^{7, 15}

In addition to such drugs, certain general therapeutic measures should be emphasized. The avoidance of fatigue must be stressed, and reassurance is constantly necessary. Physiotherapy, narcotics, anesthetics, quinine, curare, and desiccated thyroid should be avoided since they may exaggerate the myasthenic condition. During exacerbations careful nursing attention is necessary.

Two new agents, di-isopropylfluorophosphate and tetraethyl pyrophosphate, are being used experimentally.^{6, 18} Presumably the potent toxic effect of fluorine on enzyme systems inactivates cholinesterase.⁶ Preliminary clinical reports of di-isopropylfluorophosphate and tetraethyl pyrophosphate indicate good clinical results. Tetraethyl pyrophosphate is the least toxic, but the margin between the effective

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dose and the dangerous dose is narrow; and it is not as potent an inhibitor of cholinesterase as is neostigmine. More prolonged action is its chief attribute. Convulsions and gastrointestinal symptoms are the most frequent symptoms of intoxication from use of these two drugs. Both are extremely unstable in the presence of water, and dosage is difficult to maintain.¹⁶ Consequently, di-isopropyl-fluorophosphate and tetraethyl pyrophosphate need further experimental and therapeutic studies before they may be considered reliable and safe.

A few words with respect to cholinergic-stimulating therapy in myasthenia therapy may be in order. Urecholine®* (B methylcholine urethane), which has a parasympathetic-like action, was suggested to the authors as an adjuvant in myasthenia gravis. This drug is stable and has a prolonged action in producing nicotine-like effects.¹⁷ It is less toxic than other choline derivatives. Electromyographic studies following subcutaneous injection of Urecholine (0.5 mg.) in patients with myasthenia showed an increase in muscle action potentials similar to those observed after neostigmine. Although the observed response was weaker than the response obtained with neostigmine, it was more prolonged, which suggests that Urecholine may be a useful adjuvant to neostigmine therapy in myasthenia gravis. Clinical studies of the drug which are being made by the authors are still in an initial phase, however, and results thus far do not permit an evaluation of the usefulness of this agent in myasthenia gravis.

A review of the therapy of myasthenia gravis would not be complete without some mention of the recent studies on the thymus gland. Treatment of the thymus has involved two approaches, radiation and operation. The presence of a thymic tumor, as demonstrated by x-ray in patients with myasthenia gravis, by no means justifies thymectomy. The results of thymectomy have been variable, and since spontaneous remission occurs in approximately 25 per cent of myasthenic patients, the results of thymectomy are difficult to evaluate.¹¹ In addition, it must be remembered that the estimated mortality of thymectomy is from 20 to 25 per cent and that only some 25 or 30 per cent of myasthenic patients are suitable subjects for the operation. Thus, thymectomy is not only hazardous,¹³ but its effects are equivocal. The recent reports of Clagget and Eaton,⁵ Blalock,² Keynes,¹³ Harvey,¹¹ and Castleman and Norris⁴ lead to the conclusion that final evaluation of thymectomy in myasthenia gravis will require further study. The results of radiation therapy on the thymus gland have also been equivocal.

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